REMARKS

Claims 158, 179, and 200 have been amended. No new matter has been added by way of amendment. Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205, and 208 will be pending upon entry of the instant amendment.

Statement of Summary of Interview

Applicants appreciated the opportunity to discuss the rejection of record and art with Examiner Kolker by telephonic interview. On August 16, 2007, Applicant's representatives Jon Hamm and Mario Cloutier (both patent agents) discussed the outstanding 35 U.S.C. §103 rejection and prior art cited, as well as the post-filing reference Roschke et al. Agreement was not reached, but the Applicants thank the Examiner for his time and consideration.

Election/Restrictions

Applicants appreciate withdrawal of the species election with respect to a single species of chemokine.

Double Patenting

Claims 147, 150-153, 155-156, 158, 160-163, 165-166, 168, 171-174, 176-177, 179, 181-184, 186-187, 189, 192-195, 197-198, 200, 202-205, and 207-208 were rejected by the Examiner under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 6,528,625. Specifically, the Examiner argued that the "instant claims are rendered obvious in view of the '625 patented claims directed to HB-12366 (2D7) antibody, antigen binding fragment, antibody producing hybridoma, compositions and test kit with properties including all limitations as instantly recited."

As stated in the response of November 28, 2005, Applicants will file a Terminal Disclaimer to overcome the Examiner's obviousness-type double patenting rejection as appropriate upon notice of otherwise allowable subject matter in the present application. This will permit Applicants to assess the appropriateness of the rejection in view of the claims as ultimately indicated to be allowable, since it is possible that the claims may change during the course of prosecution.

Priority

Applicants note that the Examiner has given all pending claims the priority date of July 11, 1997.

The Rejection of Claims under 35 USC §103(a) Should Be Withdrawn

Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205, and 208 were rejected by the Examiner under 35 U.S.C. §103(a) as unpatentable over Li et al. (U.S. Patent 6,025,154), Li et al. (U.S. Patent 6,759,519), Raport et al. (*J. Biol. Chem.*, 271(29):17161-17166, 1996), Combadiere et al. (*J Leukocyte Biol.*, 60:147-152, 1996), Samson et al. 1996 (*Biochemistry*, 35:3362-3367, 1996), as evidenced by Wu et al. (*J. Exp. Med.* 186(8):1373-1381, 1997), Atchison et al. (*Science*, 274 :1924-1926, 1996), and Samson et al. 1997 (*J. Biol. Chem.*, 272(40): 24934-24941, Oct. 1997).

The Rejection of Record

The Examiner concludes that the claimed antibodies and antigen binding fragments are obvious because Li et al. suggest that antibodies that bind CCR5 and inhibit ligand binding can be identified using suitable screening assays, and that Raport et al., Combadiere et al and Samson et al. disclose that MIP-1α, MIP-1β, and RANTES are ligands for CCR5. The Examiner asserts a number of times that the claimed antibodies and antigen binding fragments are obvious because a screen to identify antibodies which inhibit ligand binding to CCR5 would necessarily identify antibodies that bind to the second extracellular loop and inhibit HIV infection, and that both such characteristics are evidenced as mapping to the same site, and therefore must be features of all anti-CCR5 antibodies that bind to the second extracellular loop and/or inhibit ligand binding.

The Examiner believes that the three secondary references, namely Wu et al., Atchison et al. and Samson et al. provide evidence that the claimed properties of the antibodies and antigen binding fragments are inherent, and that the claimed antibodies would necessarily be identified by a screen for antagonists to CCR5 ligand binding according to Li et al. The Examiner asserts that Samson et al. (1997), Atchison et al., and Wu et al. provide evidence that the chemokine binding site of CCR5 is also the site of HIV binding, and that the second extracellular loop of CCR5 is critical to HIV infection.

The Examiner stated:

> [T]he art of record supports the conclusion that antibodies specific for inhibition of ligand binding and receptor function would be specific to the second extracellular loop and would also inhibit HIV binding/entry.

> Accordingly, the screening assay of Li when practiced with MIP-1alpha, beta and RANTES ligands as suggested by Samson (AV), Combadiere (AT3) and Raport (AW) would necessarily result in the identification of antibodies specific to the second extracellular loop, i.e. the chemokine binding and signaling site. That this site is also evidenced as the major co-receptor allowing infection of HIV is further evidenced as noted via Samson 1997 and Atchison 1996 AZ5. Hence, the screening assay of Li would identify antibodies capable of inhibiting infection of HIV as the ligand binding site of the second extracellular loop is critical to HIV infection. Both properties are evidenced as mapping to the same site, i.e. within the second extracellular loop.

(Office Action, page 12, Emphasis added). Applicants traverse the rejection and submit that the claimed invention is non-obvious over Li et al. (U.S. Patent Nos. 6,025,154 and 6,759,519), Raport et al., Combadiere et al., and Samson et al. (1996), as evidenced by Wu et al., Atchison et al., and Samson et al. (1997). Applicants submit that the skilled artisan at the time of filing, even with an arguably high level of skill in generation of antibodies, would have no reasonable expectation of success in making antibodies that bind CCR5 and inhibit both chemokine ligand binding and HIV infection.

Primary References

Li et al. teaches a human HDGNR10 that is the same as human CCR5. Li et al. suggests making antibodies to CCR5. Li et al. suggests that agents that inhibit ligand binding to CCR5, or that inhibit receptor function associated with ligand binding can be identified by screening. However, Li et al. does not present any working examples of antibodies to CCR5. Li et al. does not teach or suggest any ligand(s) to CCR5, nor does Li et al. make any mention of the second extracellular loop of CCR5 or any HIV binding region of CCR5.

Raport et al., Combadiere et al., and Samson et al. (1996) are all CCR5 cloning papers identifying MIP-1α, MIP-1β, and RANTES as ligands for CCR5. However, none of Raport et al., Combadiere et al., and Samson et al. (1996) teaches or suggests any importance of the second extracellular loop of CCR5 for ligand binding, HIV infection or in any role.

With respect to the teachings of Raport et al., the Examiner asserted that,

> Raport et al. (AW) notes that, 'this same combination of chemokines has recently been shown to potently inhibit human immunodeficiency virus replication in human peripheral blood leukocytes,' see in particular abstract noting others with direction to the N-terminus and second extracellular loop as important in mediating HIV infection.

(Office Action, page 10. Emphasis added.)

This characterization of the teachings of Raport et al. is factually incorrect. Raport et al. is silent, in the abstract and throughout, with respect to portions of CCR5 that might be important in mediating HIV infection. While Raport et al. cites a reference that investigated the effect of the CCR5 ligands themselves (MIP-1α, MIP-1β, and RANTES) on HIV infection, it contains no teaching, suggestion or reference to work by others as to which portions of CCR5 are involved in ligand or HIV binding. That a chemokine ligand of a receptor inhibits HIV infection via binding to that receptor does not necessarily suggest that blocking binding of that ligand would have the same effect as causing the ligand to bind.

Secondary References

Atchison et al. does not teach or suggest that the second extracellular loop of CCR5 is important for HIV infection. Nor does Atchison et al. provide evidence that inhibition of HIV infection is inherent in antibodies to CCR5 that inhibit chemokine binding to CCR5. In fact, Atchison et al., at page 1925, first column, states that receptor chimeras containing the second extracellular loop of CCR5 "repeatedly had no coreceptor function" for HIV infection and that "substitution of the NH2-terminal segment from CCR5 (5222) conferred robust susceptibility to HIV-1 cell entry" (Emphasis added). Furthermore, Atchison et al. state, "viral coreceptor activity is dissociable from ligand dependent responses". Thus, Atchison et al. demonstrates that an antibody that binds the second extracellular loop of CCR5 would not necessarily also inhibit HIV infection. The teachings of Atchison et al. might indicate that an antibody that binds the NH2-terminal of CCR5 would be expected to inhibit HIV infection because the reference teaches that the "NH2-terminal segment [of CCR5] confers robust susceptibility to HIV-1 cell entry," but this is not the claimed invention. Thus, Atchison et al. teaches away from the second extracellular loop as important in HIV binding and infection.

The Samson et al.(1997) and Wu et al. references cited in the statement of rejection are not prior art, and the teaching of these references were not available to the person of ordinary skill in the art at the time the invention was made.

Samson et al. (1997) is a post-filing reference, and thus is not prior art. Regardless, the only teachings in Samson et al. (1997) with respect to CCR5 and HIV infection are that both the N-terminus and the first extracellular loop of CCR5 are important in HIV binding/infection (please see page 23934, second column, first full paragraph) and that "regions of CCR5 involved in chemokine ligand specificity, and in the specificity of cofactor usage for various HIV-1 strains are not identical," (see page 24940, paragraph spanning first and second columns). Thus, Samson et al. (1997) provides no evidence that an antibody that binds the second extracellular loop of CCR5 would necessarily and inevitably also inhibit

HIV infection. In fact, the plain teachings of this reference indicate that an antibody that binds the second extracellular loop of CCR5 would not inhibit HIV infection because such an antibody would not bind to the regions of CCR5 that are taught to be involved in HIV infection.

Neither Samson et al. nor Atchison et al. provides evidence that an antibody that binds the second extracellular loop of CCR5 and inhibits chemokine ligand binding to CCR5 would inherently also inhibit HIV infection.

Wu et al., like Samson et al. 1997, is not prior art. Wu et al. is a later scientific publication of Applicant's own invention. Therefore, Wu et al. is only being used to provide improper hindsight or as evidence of inherency.

Wu et al. studied a panel of anti-CCR5 antibodies for their ability to inhibit either chemokine binding or HIV-1 gp120 binding and HIV-1 infection. Wu et al. teaches anti-CCR5 antibodies, including one named 2D7 that inhibits chemokine ligand binding and binds the second extracellular loop of CCR5. However, Wu et al. still fails to show that all antibodies that bind the second extracellular loop, or block chemokine ligand binding, would inherently also inhibit HIV infection.

Using chimeric CCR2b/CCR5 receptors, Wu et al. mapped the domains on CCR5 recognized by the panel of mAbs and correlated inhibitory activity with domain specificity of the mAbs. Wu et al. teaches that the second extracellular loop of CCR5 is the main chemokine binding determinant of CCR5.

In addition, Wu et al. teaches that binding of HIV to CCR5 is more complex than ligand binding, and discloses that inhibition of HIV binding to CCR5 could be achieved with mAbs "recognizing **either** the **second extracellular loop or** the **NH_2-terminal region**." (see Wu et al., abstract, Emphasis Added). Thus, *inter alia,* the teachings of Wu et al. highlight the *diversity* of anti-CCR5 antibodies capable of inhibiting HIV infectivity. For example, Wu et al. discloses an antibody named 3A9, which reacted only with chimeras that contained the NH_2-terminal region of CCR5, and that this 3A9 antibody exhibited significant inhibition of HIV infection, as determined by inhibition of ^{125}I-gp120 binding (please see page 1375, paragraph spanning both columns; pages 1377-1378 and Figure 6A).

Applicants therefore submit that the claimed antibodies and antigen binding fragments are not made obvious by the teachings of the prior art references, because the art does not provide a reasonable expectation of success in producing an antibody that (1) binds the second extracellular loop of CCR5, (2) inhibits binding of MIP-1α, MIP-1β, or RANTES to CCR5, and (3) inhibits HIV infection. Furthermore, Samson et al. (1997), Atchison et al., and Wu et al. fail to provide evidence that antibodies that bind the second extracellular loop of CCR5 and inhibit chemokine ligand binding to CCR5 would inherently also inhibit HIV infection.

Objective Evidence that the Claimed Features are Not Inherent

The Examiner is again asked to consider the post-filing objective evidence supplied by the Applicants that shows that some antibodies that bind CCR5 and inhibit chemokine ligand binding do not inhibit HIV infection, demonstrating that inhibition of chemokine ligand binding does not necessarily equate to inhibition of HIV binding/infection. Roschke et al. (poster; submitted in Supplemental IDS mailed June 27, 2006 as citation number BU) generated a large panel of monoclonal anti-CCR5 antibodies and examined the ability of these antibodies to bind CCR5, inhibit MIP-1β binding to CCR5, and to inhibit HIV viral entry (please see abstract, results section, and Figure 1 of Roschke et al). Roschke et al. noted "interestingly, while the most potent inhibitors of HIV-1 infection were effective at blocking chemokine binding, the ability to block chemokine binding and to block HIV-1 infection were **not mutually inclusive** (Figure 1)". (Emphasis added).

Importantly, Roschke et al. disclose at least four antibodies in Figure 1 which inhibit MIP-1β binding potently, but which do not inhibit HIV viral entry (Figure 1, especially CCR5 mAbs 20, 33, 37 and 38). For example, anti-CCR5 mAbs 20, 33, 37 and 38 each have an IC_{50} for inhibiting MIP-1β binding which is similar to or lower than the antibody chosen for further focus, mAb004 (i.e. 0.80, 0.04, 0.50, and 0.50 nM versus 0.41 nM for mAb004) but do not inhibit HIV viral entry. Thus, anti-CCR5 antibodies capable of binding the second extracellular loop of CCR5 and inhibiting ligand binding are not necessarily capable of also inhibiting HIV infection.

Therefore, Roschke et al. provides evidence that antibodies identified by a screen suggested by Li et al., directed to identifying antibodies which inhibit chemokine ligand binding to CCR5, would not necessarily also have the characteristic of inhibiting HIV infection.

The Examiner states that Roschke et al. does not distinguish if any of the antibodies that are noted to inhibit chemokine binding also inhibit one or more functions associated with binding of that chemokine, and seems to require that inhibition of both binding and such function(s) be dissociated from inhibition of HIV infection, in order for the claimed antibodies to be non-obvious over the prior art (September 18, 2006 Office Action, pages 16-17). In an effort to expedite prosecution, Applicants have amended the base claims 158, 179, and 200 in order to remove the limitation, "wherein said antibody or antigen binding fragment inhibits one or more functions associated with binding of the chemokine to the receptor". Thus, the claims as amended are commensurate in scope with the evidence set forth in Roschke et al. In other words, Roschke et al. serves as evidence that not all antibodies that bind the second extracellular loop of CCR5 and inhibit chemokine ligand binding to CCR5 necessarily also inhibit HIV infection, as the claimed antibodies do.

To summarize, antibodies or antigen-binding fragments thereof which

1) bind to the second extracellular loop of a human CCR5, and

2) inhibit binding of MIP-1α, MIP-1β, or RANTES to the receptor,

do not necessarily have the ability to

3) additionally inhibit HIV infection.

The claimed antibodies and antigen binding fragments are not obvious because antibodies identified by a screen suggested by Li et al., directed to identifying agents which inhibit chemokine binding to CCR5, would not necessarily and inevitably also have the characteristic of inhibiting HIV infection.

Li et al., Raport et al., Combadiere et al., and Samson et al. (1996), do not teach or suggest all of the limitations of the instant claims, either alone or in combination, and one of ordinary skill in the art would not have had a reasonable expectation of success in making antibodies with all of the claimed limitations. Wu et al., Atchison et al, and Samson et al. (1997) fail to demonstrate that combination of Li et al., Raport et al., Combadiere et al., and Samson et al. (1996) would necessarily result in the production of antibodies that have the claimed characteristics, or actually teach away from such limitations. Roschke et al. gives actual examples of antibodies that bind CCR5 and inhibit chemokine ligand binding to CCR5 but which do not inhibit HIV infection, showing that inhibition of HIV infection is not an inherent characteristic of an anti-CCR5 antibody which inhibits chemokine ligand binding to CCR5. Roschke et al. shows that antibodies to CCR5 that might be identified in a screen suggested by Li et al. do not inherently and inevitably have all the limitations of the claimed invention.

Accordingly, in absence of evidence to the contrary, there is no credible scientific reasoning or evidence to support the Examiner's assertion that the allegedly inherent characteristic ("wherein the antibody of antigen binding fragment thereof additionally inhibits HIV infection") is inherently and inevitably a feature of all the postulated antibodies identified by a screen suggested by Li et al. for antagonists that inhibit chemokine binding to CCR5. Roschke et al. provides evidence showing that the prior art products (or more specifically, postulated antibodies identified by a screen allegedly suggested by Li et al.) do not necessarily possess the characteristics of the claimed product.

Thus, the presently claimed invention is non-obvious over the cumulative reference teachings of the art cited by the Examiner.

Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection of claims under 35 USC §103(a).

CONCLUSION

In view of the remarks and amendments made herein, Applicants respectfully submit that the rejections presented by the Examiner are now overcome and that this application is in condition for allowance. If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

This paper is being filed timely as a request for five month extension from the Notice of Appeal is filed concurrently herewith, along with a Request for Continued Examination. Applicants believe no further extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

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